
Citation:

Nichols, S and Taylor, C and Ingle, L (2015) A clinician's guide to cardiopulmonary exercise testing 2: test interpretation. British Journal of Hospital Medicine, 76 (5). pp. 281-289. ISSN 1750-8460
DOI: <https://doi.org/10.12968/hmed.2015.76.5.281>

Link to Leeds Beckett Repository record:

<https://eprints.leedsbeckett.ac.uk/id/eprint/3124/>

Document Version:

Article (Accepted Version)

The aim of the Leeds Beckett Repository is to provide open access to our research, as required by funder policies and permitted by publishers and copyright law.

The Leeds Beckett repository holds a wide range of publications, each of which has been checked for copyright and the relevant embargo period has been applied by the Research Services team.

We operate on a standard take-down policy. If you are the author or publisher of an output and you would like it removed from the repository, please [contact us](#) and we will investigate on a case-by-case basis.

Each thesis in the repository has been cleared where necessary by the author for third party copyright. If you would like a thesis to be removed from the repository or believe there is an issue with copyright, please contact us on openaccess@leedsbeckett.ac.uk and we will investigate on a case-by-case basis.

A Clinician's Guide to Cardiopulmonary Exercise Testing: Part 2 – Test Interpretation

Simon Nichols¹, Claire Taylor¹, Lee Ingle^{1*} PhD

**¹Department of Sport, Health and Exercise Science, University of Hull, Kingston-upon-Hull,
HU6 7RX**

*Address for correspondence

¹003 Don Building

Department of Sport, Health & Exercise Science

University of Hull

Cottingham Road

Kingston-upon-Hull

HU7 6RX

United Kingdom

Tel: 01482 463141

Fax: 01482 463855

Email: L.Ingle@hull.ac.uk

Keywords: Cardiovascular disease, CPET, CPX, Risk stratification, Heart disease, Myocardial ischaemia.

Data obtained from cardiopulmonary exercise testing offers additional interpretive power over conventional exercise tolerance testing. When used correctly, it allows improved clinical decision-making in patients with cardiometabolic and respiratory disease.

Introduction

The following article is the conclusion to our recently published ‘...Clinician’s Guide to Cardiopulmonary Exercise Testing: Part 1 – An Introduction’ (Taylor et al., 2015) summarising the preparatory requirements for cardiopulmonary exercise testing (CPET). This article will focus on the interpretation of a CPET and how to accurately apply findings for the purposes of patient diagnosis and risk stratification. Readers are reminded that CPET should be treated as any other medical investigation and every care should be taken to ensure rigorous calibration and test preparation. Failure to do so will compromise data accuracy resulting in reduced test sensitivity and specificity.

Interpretation of CPET data

Peak oxygen uptake

Peak oxygen uptake ($\dot{V}O_{2\text{peak}}$) reflects the body’s maximal capacity to generate energy through aerobic metabolism. It can be defined using the Fick equation:

$$\dot{V}O_2 = Q \times (a-vO_2 \text{ diff})$$

Where Q is cardiac output and $a-vO_2 \text{ diff}$ is the difference between arterial and venous oxygen content. $\dot{V}O_2$ is normally reported in absolute terms ($L \cdot \text{min}^{-1}$) or relativised to body mass ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and plotted as a function of time or workload (plot 1 of the 9-panel plot). Peak oxygen uptake is an independent predictor of mortality and has wide clinical application. The seminal paper by Mancini and colleagues (1991) was amongst the first to identify a threshold based on $\dot{V}O_{2\text{-peak}}$ data ($<14 \text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) which could be used to guide clinical decision making for cardiac transplantation in patients with left ventricular systolic dysfunction. Indeed, $\dot{V}O_{2\text{peak}}$ is an integral component of the Heart Failure Survival Score

[HFSS] (Aaronson et al., 1997) and is listed in the current UK guidelines (Box 1) as criteria for referral and assessment of adults for cardiac transplantation (Banner et al., 2011).

Box 1: Conventional Criteria for Heart Transplantation

- Impaired LV systolic function
- NYHA III (e.g. patient cannot climb one flight of stairs without symptoms) or IV symptoms
- Receiving optimal medical treatment (including target or maximum tolerated doses of β -adrenergic antagonists, ACE inhibitors and aldosterone antagonists)
- CRT, ICD or CRTD device implanted (if indicated)
- Evidence of a poor prognosis, for example,
 - i. Cardiorespiratory exercise testing ($\text{VO}_{2\text{max}}$ <12 ml/kg/min if on β -blockade, <14 ml/kg/min if not on β -blockade, ensuring respiratory quotient ≥ 1.05)
 - ii. Markedly elevated BNP (or NT-proBNP) serum levels despite full medical treatment
 - iii. Established composite prognostic scoring system, such as the HFSS or SHFM

BNP, B-type natriuretic peptide; CRT, cardiac resynchronisation treatment; CRTD, CRT and ICD treatment; $\text{VO}_{2\text{max}}$, maximal oxygen uptake HFSS, Heart Failure Survival Score; ICD, implantable cardioverter defibrillator; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA class IV, New York Heart Association; SHFM, Seattle Heart Failure Model.

Furthermore, Weber and colleagues (1982) developed a classification system for grading the severity of chronic heart failure (CHF), suggesting $<10 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and $>18 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ to be indicative of high and low risk groups.

Integrated into most contemporary metabolic carts are decision tree algorithms designed to assist with diagnosing the cause of any exercise limitation (Wasserman et al., 2011). The first decision is to determine whether $\dot{V}\text{O}_{2\text{peak}}$ is abnormally low ($<75\%$ of predicted $\dot{V}\text{O}_{2\text{max}}$) as defined by Wasserman and colleagues (2011). However, a low $\dot{V}\text{O}_{2\text{peak}}$ may be due to poor patient effort, therefore criteria for evaluating maximal effort should always be

considered (Box 2). Alternatively, abnormally low $\dot{V}O_{2\text{ peak}}$ may suggest a cardiovascular limitation due to reduction in cardiac output, arterial O_2 content, muscle oxygen extraction, and/or ineffective vascular shunt. Although $\dot{V}O_{2\text{ peak}}$ quantifies cardiorespiratory fitness (CRF), it does not indicate the cause of an exercise limitation and it is necessary to conduct further assessment to determine any underlying pathophysiology.

Cardiopulmonary exercise tests are often conducted in patients with a known clinical diagnosis. In these circumstances a lower $\dot{V}O_{2\text{ peak}}$ may be expected, therefore it may be useful to compare test results with “normative” values for a specific patient group. Table 1 illustrates how CPET can distinguish between different pathologies by comparing a healthy individual with a CHF and chronic obstructive pulmonary disease patient. Whilst $\dot{V}O_{2\text{ peak}}$ is considered by many to be the primary CPET-derived outcome variable, its reproducibility and prognostic power are affected by a number of factors including patient effort, test protocol design, familiarity, and disease severity. Alternative markers of aerobic capacity such as the ventilatory anaerobic threshold (VAT) can be used to improve prognostic power and assist in the quantification of CRF.

Box 2: Maximal Effort Criteria

- Failure of HR to increase with further increases in exercise intensity (achieving $\geq 85\%$ of age-predicted maximal HR is a well-recognised indicator of patient effort)
- A plateau in $\dot{V}O_2$ (or failure to increase by $150\text{ mL}\cdot\text{min}^{-1}$) with an increased workload
- A respiratory exchange ratio ($\text{RER} = \dot{V}CO_2 / \dot{V}O_2$) at peak exercise ≥ 1.10
- A rating of perceived exertion (RPE) > 17 on the 6-20 Borg scale or > 9 on the 0-10

Table 1. Interpretation of CPET data for a healthy male (Figure 1); a patient with chronic heart failure (Figure 2); a patient with emphysema and mild-moderate obstructive lung disease (Figure 3).

PLOT	HEALTHY (FIG 1)	CHF (FIG 2)	COPD (FIG 3)
PLOT 1	Peak VO ₂ within normal predicted range (102% of predicted)	Peak VO ₂ low (52% of predicted)	Peak VO ₂ low (63% of predicted)
	Δ VO ₂ / Δ WR slope normal (9.8ml/min/W)	Δ VO ₂ / Δ WR slope low (5.7ml/min/W)	Δ VO ₂ / Δ WR slope low (7.3 ml/min/W)
PLOT 2	Normal O ₂ /HR (97% of predicted)	O ₂ /HR flattens after 2 minutes of exercise	Normal O ₂ /HR (84% of predicted)
	Normal peak HR (107% of predicted)	Peak HR low (56% of predicted)	HRR High
PLOT 3	VAT normal (49% of predicted VO _{2peak})	VAT low (38% of predicted VO _{2peak})	VAT low (41% of predicted VO _{2peak})
PLOT 4	Normal ventilatory equivalents	VE/VCO ₂ at VAT high (44) Suggesting elevated V _D /V _T	Ventilatory equivalents high (increased V _D)
PLOT 5	N/A	N/A	N/A
PLOT 6	Normal (<34)	Elevated	Elevated
PLOT 7	Normal partial pressures	Normal SPO ₂	SPO ₂ Low at peak (88%)
PLOT 8	Normal RER	Normal RER	Normal RER
PLOT 9	Normal BR (93)	Normal BR (39)	Low BR (2)

CPET, Cardiopulmonary exercise test; CHF, Chronic heart failure; VO₂, Oxygen uptake; Δ VO₂, Delta oxygen uptake; Δ WR, Delta work rate; COPD, Chronic obstructive pulmonary disease; HR, Heart rate; HRR, Heart rate reserve; VAT, Ventilatory anaerobic threshold; VE, Minute ventilation; V_D, Ventilatory dead space; V_T, Ventilatory tidal volume; SPO₂, Arterial oxygen saturation; RER, Respiratory exchange ratio; BR, Breathing reserve

Ventilatory Anaerobic Threshold (VAT)

During CPET, $\dot{V}O_2$ and expired carbon dioxide ($\dot{V}CO_2$) increase linearly until the point where oxidative metabolism can no longer sustain the required workload. Anaerobic glycolysis is increasingly required for energy synthesis to maintain higher work rates leading to increased blood lactate accumulation. Bicarbonate buffering of associated H^+ ions results in increased CO_2 production that is ventilated to maintain pH balance. This causes a breakpoint in the linear relationship between $\dot{V}O_2$ and $\dot{V}CO_2$ as shown in plot 3 the 9-panel plot. This point marks the VAT (also known as VT_1).

The V-slope method is perhaps the most widely used technique for VAT determination (Beaver et al., 1986, Wasserman et al., 2011) and is achieved by plotting $\dot{V}CO_2$ as a function of $\dot{V}O_2$. A trend line is drawn through the plots from the initiation of exercise to the point at which the linear relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ is lost (Slope slightly less than 1). A second trend line can then be drawn from the end of the test through to the deflection point. The point at which these two lines bisect indicates the VAT; a value in $ml \cdot kg^{-1} \cdot min^{-1}$ should be reported which can then be calculated as a percentage of $\dot{V}O_{2\text{ peak}}$.

The ventilatory anaerobic threshold is considered a reliable marker of aerobic capacity since a low VAT indicates decreased O_2 transport chain efficiency. Patients with superior CRF will have a VAT closer to their $VO_{2\text{ peak}}$, however for most patients VAT will lie between 40-60% of their peak aerobic capacity.

A VAT <40% of peak $\dot{V}O_2$ (or predicted $\dot{V}O_{2\text{ max}}$) is indicative of disease pathology or significant physical deconditioning (Mezzani et al., 2009). A VAT <11 $ml \cdot kg^{-1} \cdot min^{-1}$ is commonly used to identify patients at higher peri-operative risk and is associated with a 5.3 fold increase in mortality (Gitt et al., 2002). However, many CHF patients have heterogeneous muscle fibre types, abnormal metabolism and compromised exercise haemodynamics. These abnormalities preclude the detection of VAT with non-detection indicative of poor prognosis (Agostoni et al., 2013).

With increasing exercise intensity above the VAT, intracellular bicarbonate is no longer able to adequately offset metabolic acidosis. At this point an increase in VE in excess of VCO₂ can be observed and marks the ventilatory compensation point (also referred to as VT₂).

Ventilatory Compensation Point

The ventilatory compensation point (VCP) is a marker of the upper limit of sustainable aerobic exercise effort and therefore like VAT and $\dot{V}O_2$ peak, is an important parameter describing O₂ transport and utilisation. It is usually attained at approximately 70–80% VO₂peak and 80–90% HR peak (Mezzani et al., 2013). The VCP is well-correlated to 'critical power' (Dekerle et al., 2003) representing the highest power sustainable in conditions of both VO₂ and lactate steady state (i.e. at the limit between high and very-high exercise intensity domains). The VCP is identifiable in plot 6 of the 9-panel plot as an inflection in VE vs $\dot{V}CO_2$ or inflection in VE/ $\dot{V}CO_2$ (plot 4) with a concurrently occurring deflection point in end-tidal CO₂ (PETCO₂; plot 7). It is important to note that a VCP may not be identifiable in patients who have failed to achieve a near-maximal effort during CPET.

VE/VCO₂ slope

The slope of the relationship between VE and $\dot{V}CO_2$ (VE/ $\dot{V}CO_2$ slope) during incremental exercise describes ventilatory efficiency and quantifies the ventilatory rate required to eliminate 1 litre of CO₂ (plot 6 of the 9 panel plot). If an inappropriately high ventilatory response, caused by hyperactive peripheral chemoreceptors or increased V_D/V_T is present, PaCO₂ will drop and the VE/ $\dot{V}CO_2$ slope will steepen. Muscle ergoflex activation is also a proposed mechanism of increased VE/ $\dot{V}CO_2$ slope in patients with CHF. Mathematically, the VE/ $\dot{V}CO_2$ slope is determined by 3 factors: the amount of CO₂ produced; the physiological

dead space/tidal volume ratio (V_D/V_T); and PaCO_2 . The relationship can be explained by the equation:

$$\text{VE} = 863 \times \dot{V}\text{CO}_2 / \text{PaCO}_2 (1 - V_D/V_T)$$

Where, 863 is a constant (corrects for different environmental conditions, and assumes core temperature of 37 °C), V_D/V_T is the physiological dead space/tidal volume ratio, and PaCO_2 is the arterial CO_2 partial pressure. A $\text{VE}/\dot{V}\text{CO}_2$ slope elevation is a phenomenon frequently observed in CHF patients (Sullivan et al., 1988) and discriminating whether this anomaly is a result of a respiratory or circulatory aetiology can be challenging. Clinical evaluation of past medical history and presenting diagnosis may help distinguish the likely cause.

A number of treatments have been shown to effectively lower $\text{VE}/\dot{V}\text{CO}_2$ slope including exercise training (Guazzi et al., 2004), angiotensin converting enzyme (ACE) inhibitors (Guazzi et al., 1999), cardiac resynchronisation therapy (Malfatto et al., 2005) and heart transplantation (Carter et al., 2006). Serial CPET may be advantageous in assessing the efficacy of such therapeutic interventions. Most contemporary metabolic carts provide automated analysis of $\text{VE}/\dot{V}\text{CO}_2$ slope however the slope can be calculated by linear regression when plotting VE as a function of $\dot{V}\text{CO}_2$. The mathematical method used to calculate this variable may make it more reproducible (Bensimhon et al., 2008) than $\dot{V}\text{O}_{2\text{peak}}$ although adequate reproducibility data remains elusive. Table 1 illustrates the differences in $\text{VE}/\dot{V}\text{CO}_2$ slope observed in a healthy male, a patient with CHF and a patient with chronic obstructive pulmonary disease (COPD). A $\text{VE}/\dot{V}\text{CO}_2$ slope >34 is commonly accepted as indicating poorer prognosis (Gitt et al., 2002, Arena et al., 2005, Ingle, 2007), although it is possible to further risk stratify patients according to a ventilatory classification system proposed by Arena et al (2007a). $\text{VE}/\dot{V}\text{CO}_2$ slope may also have a predictive role in the risk assessment of patients with coronary heart disease [CHD] (Van de Veire et al., 2006).

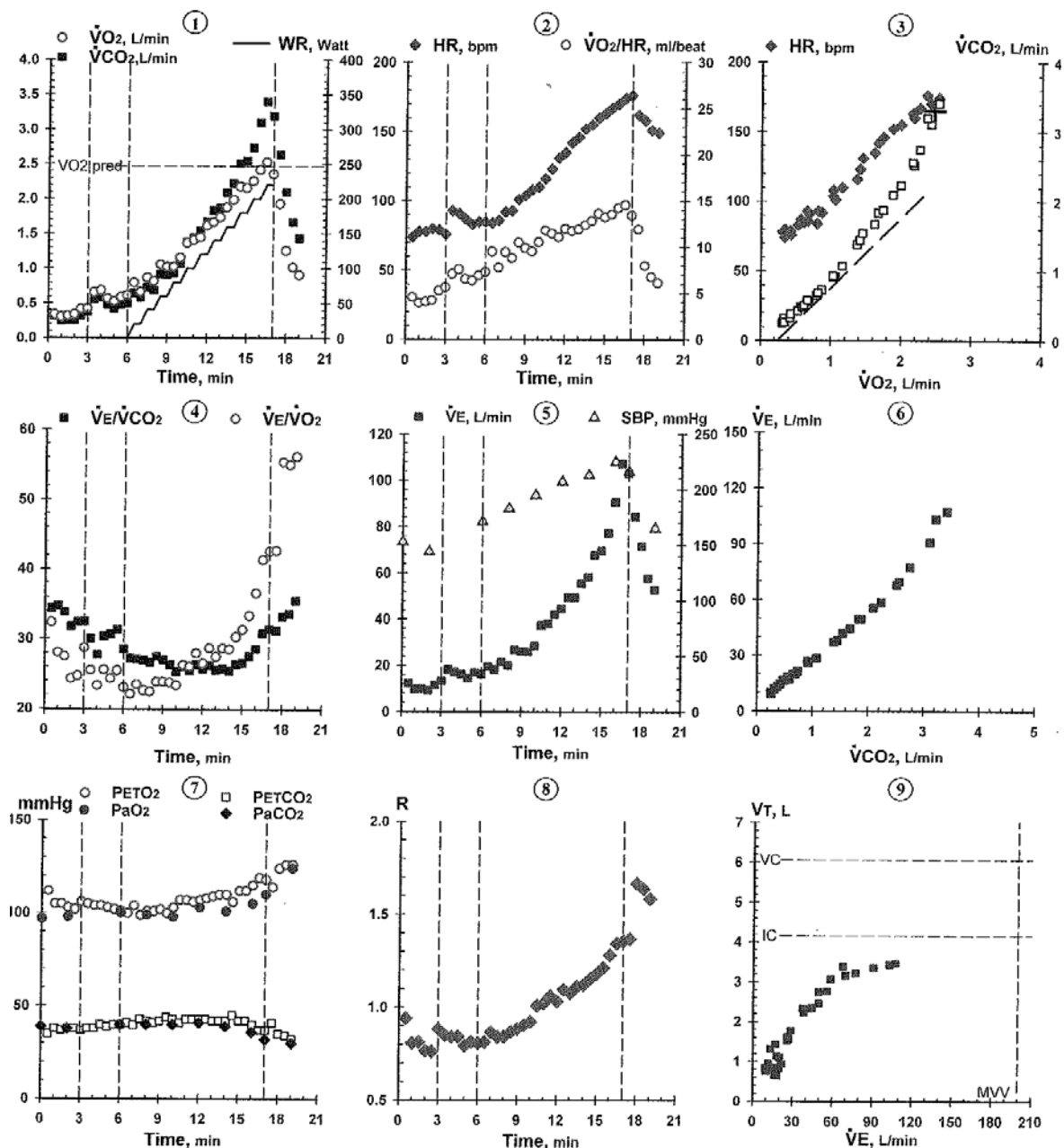


Figure 1. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, Karlman Wasserman, James Hansen, Kathy Sietsema, Darryl Y. Sue, William W. Stringer, Xing-Guo Sun, Brian J. Whipp ; Figure 10.1.1, Normal Male, 2011 $\dot{V}O_2$, Oxygen uptake; $\dot{V}CO_2$, Expired carbon dioxide; WR, Work rate; HR, Heart rate; VE, Minute ventilation; SBP, Systolic blood pressure; VT, Ventilatory tidal volume; VC, Vital capacity; IC, Inspiratory capacity; MVV, Maximum voluntary ventilation; $PETCO_2$, Partial pressure of end tidal carbon dioxide; $PETCO_2$, Partial pressure of end tidal oxygen; PaO_2 , Partial pressure of arterial oxygen; $PaCO_2$, Partial pressure of arterial carbon dioxide; R, Respiratory exchange ratio

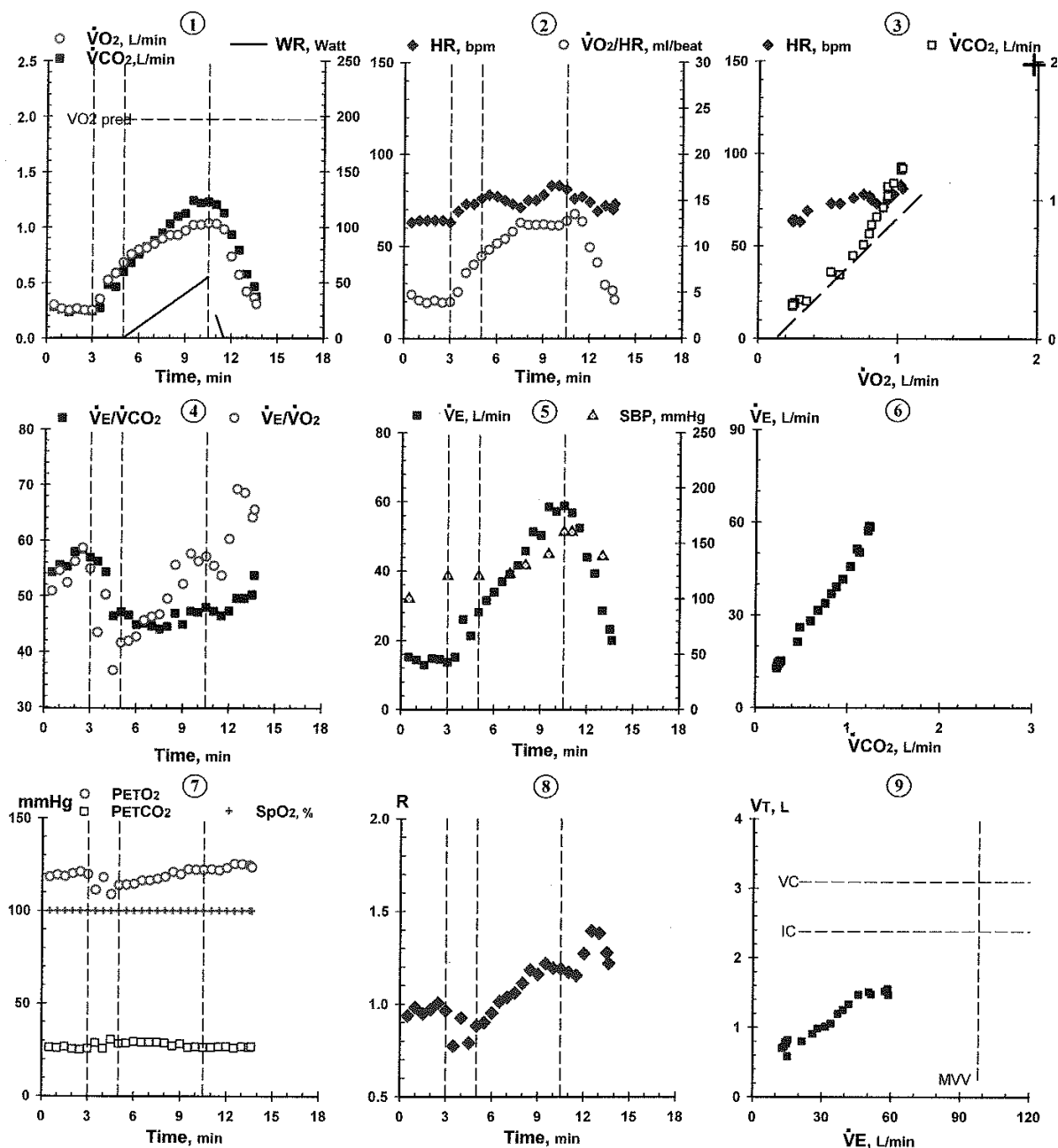


Figure 2. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, Karlman Wasserman, James Hansen, Kathy Sietsema, Darryl Y. Sue, William W. Stringer, Xing-Guo Sun, Brian J. Whipp; Figure 10.15.1, Chronic Heart Failure: Cardiomyopathy with Intraventricular Conduction Delay, 2011

$\dot{V}O_2$, Oxygen uptake; $\dot{V}CO_2$, Expired carbon dioxide; WR, Work rate; HR, Heart rate; $\dot{V}E$, Minute ventilation; SBP, Systolic blood pressure; V_T , Ventilatory tidal volume; VC, Vital capacity; IC, Inspiratory capacity; MVV, Maximum voluntary ventilation; $PETCO_2$, Partial pressure of end tidal carbon dioxide; $PETO_2$, Partial pressure of end tidal oxygen; PaO_2 , Partial pressure of arterial oxygen; $PaCO_2$, Partial pressure of arterial carbon dioxide; R, Respiratory exchange ratio

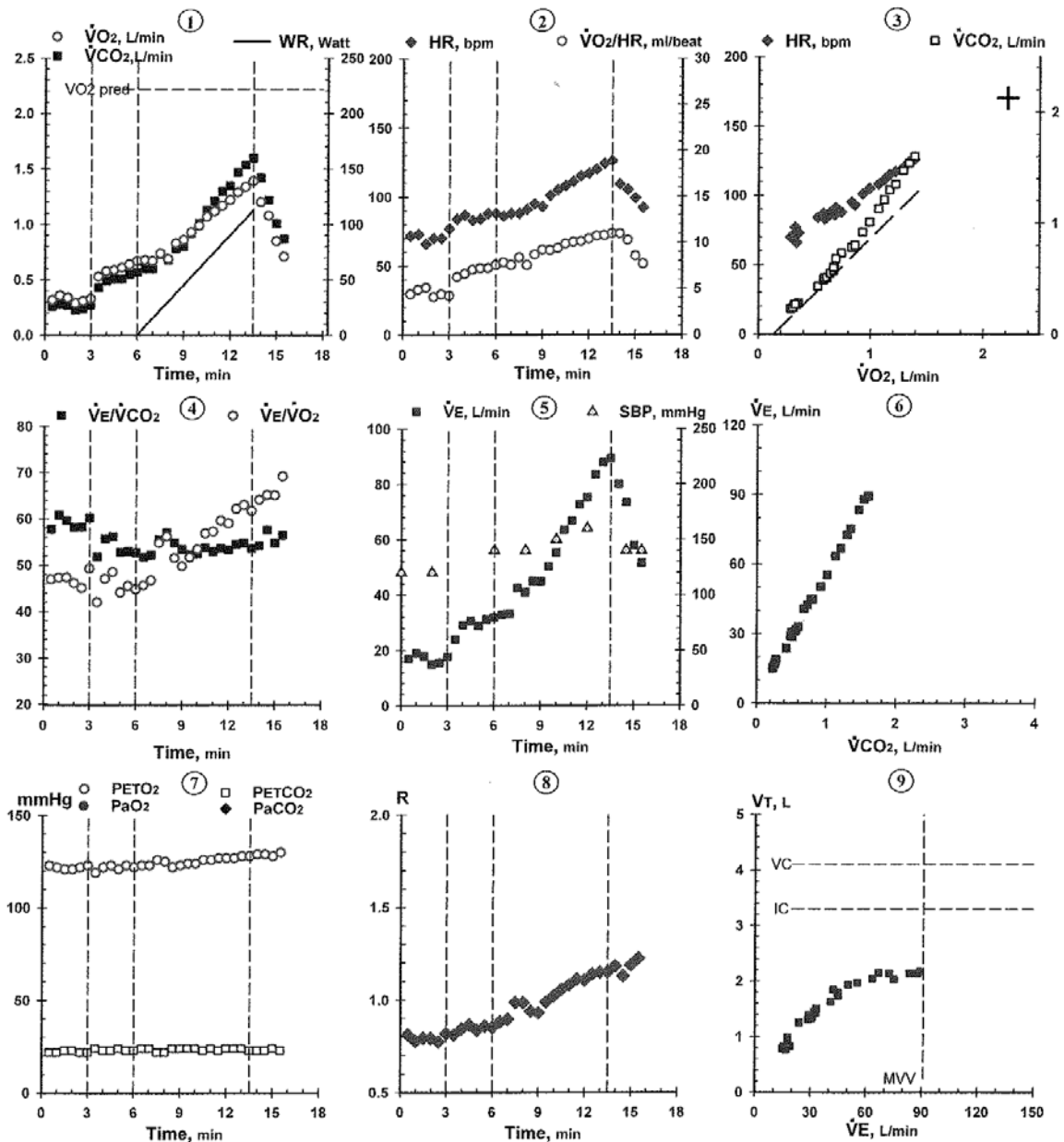


Figure 3. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, Karlman Wasserman, James Hansen, Kathy Sietsema, Darryl Y. Sue, William W. Stringer, Xing-Guo Sun, Brian J. Whipp; Figure 10.46.1, Emphysema with Mild Airway Obstruction, 2011

VO₂, Oxygen uptake; VCO₂, Expired carbon dioxide; WR, Work rate; HR, Heart rate; VE, Minute ventilation; SBP, Systolic blood pressure; VT, Ventilatory tidal volume; VC, Vital capacity; IC, Inspiratory capacity; MVV, Maximum voluntary ventilation; PETCO₂, Partial pressure of end tidal carbon dioxide; PETO₂, Partial pressure of end tidal oxygen; PaO₂, Partial pressure of arterial oxygen; PaCO₂, Partial pressure of arterial carbon dioxide; R, Respiratory exchange ratio

Measurement of circulatory function during CPET

Oxygen pulse, heart rate, and $\dot{V}O_2$ versus work rate

Exercise-induced myocardial ischaemia diagnosed through electrocardiographic (ECG) changes has poor sensitivity and specificity (Belardinelli et al., 2003). Ischaemia-induced left ventricular (LV) dysfunction however, occurs earlier in the 'ischaemic cascade' and may be detectable before ECG changes or symptoms of angina due to its deleterious effect on Q. In normal (healthy) physiology (Figure 1), Q is increased via a synergistic rise in HR and stroke volume (SV). However, ischaemia-induced LV dysfunction during exercise can lead to abrupt reductions in SV and a concurrent attenuation of Q and $\dot{V}O_2$ response during CPET.

Stroke volume can be estimated during CPET through the calculation of an exercise 'oxygen pulse' (O_2/HR ; dividing $\dot{V}O_2$ by HR (units = ml O_2 per beat)) in a modification of the Fick equation (Whipp et al., 1996). Oxygen pulse normally rises progressively throughout exercise, however a shallow rise in O_2/HR , *early* plateau or inflection (figure 2, plot 2) suggests decreasing SV with Q being partially sustained through HR compensation at the onset of myocardial ischaemia (Chaudhry et al., 2009).

Early identification of an ischaemic threshold may also be observed with greater effect by combining O_2/HR with the $\dot{V}O_2$ versus work rate slope ($\Delta\dot{V}O_2/\Delta WR$ slope). In healthy individuals, a linear $\Delta\dot{V}O_2/\Delta WR$ slope of 10ml/min/watt is maintained until peak (Figure 1; plot 1), where at the upper limits of exercise, an inflection may occur, reflecting normal physiological limitation and $\dot{V}O_2$ plateau. A uniform flattening of this relationship throughout CPET suggests a general reduction in cardiovascular efficiency (figure 2, plot 1) and may be attributed to conditions such as CHF. Cardiopulmonary exercise testing has good sensitivity and specificity in detecting exercise-induced myocardial ischaemia (87% and 74% respectively). Belardinelli and colleagues (2003) established the criteria of $\Delta\dot{V}O_2/\Delta WR$ slope inflection and concurrent O_2/HR inflection duration for the positive identification of exercise induced myocardial ischemia as compared to myocardial scintigraphy (area under the curve: 0.83). A value of 3.9ml/min/watt was selected as the strongest independent predictor of myocardial ischaemia using a hierarchical model.

The absence of $\Delta \dot{V}O_2/\Delta WR$ slope and O_2/HR inflection can be considered negative criteria for myocardial ischaemia. It should be noted however that the application of this technique may be best suited to ramp protocols or protocols with small work increments for the reasons previously explained.

Measurements of ventilatory function during CPET

Oxygen uptake efficiency slope and $VEqCO_2$ nadir

Often during clinical exercise testing, true maximal criteria are not met and we therefore use the term $\dot{V}O_{2peak}$. However, $\dot{V}O_{2peak}$ can underestimate the true cardiorespiratory reserve and other key variables such as $VE/\dot{V}CO_2$ slope lose predictive power when exercise is not conducted beyond VAT (Ingle et al., 2007, Arena et al., 2007b). Results obtained from CPET that fail to elicit satisfactory patient effort may require an alternative assessment technique.

The oxygen uptake efficiency slope (OUES) is calculated by plotting $\dot{V}O_2$ against the logarithmically transformed VE (Baba et al., 1996). The exponent of the linear relationship provides an index of oxygen uptake with respect to VE and reflects both the efficiency of oxygen delivery to the muscle and mitochondrial oxygen utilisation. OUES is only minimally altered when comparing submaximal to maximal test data (Hollenberg and Tager, 2000) with results differing by as little as 1% (Davies et al., 2006) and thus allowing an accurate index of CRF to be calculated. Furthermore the reproducibility of OUES has been shown to be superior to that of the VAT and $\dot{V}O_{2peak}$ (Van Laethem et al., 2009). An OUES of <1.4 is indicative of poor survival (hazard ratio: 4.3, 95% confidence interval: 2.4 to 7.9 p <0.001) regardless of whether VAT is reached (Arena et al., 2007b).

The $VEqCO_2$ nadir is the lowest point in the VE and CO_2 relationship when plotted over the course of a CPET and normally occurs around the VAT in most patients (plot 4). Recent work from our laboratory (Ingle et al., 2011) has shown that this variable calculated from

submaximal data has greater prognostic value than other variables collected from maximal CPET. Therefore, in patient cohorts where a maximal CPET cannot be conducted (e.g. low functional capacity groups), the OUES and VEqCO_2 nadir should be calculated to enhance risk stratification.

Exercise oscillatory ventilation

Exercise oscillatory ventilation (EOV) sometimes referred to as exercise periodic breathing (EPB) is characterised by a sino-soidal pattern of VE during incremental exercise to volitional exhaustion. It occurs in up to one third of patients with CHF and is associated with very poor outcome (Ingle et al., 2009). Whilst the genesis of EOV is unclear, two hypotheses have been postulated; the ventilatory hypothesis which is associated with abnormal chemoreceptor feedback, and the haemodynamic hypothesis which is concerned with fluctuations in cardiac output during incremental exercise.

CPET-derived prognostic scoring systems

With the advent of more powerful statistical analysis packages, there has been a move in recent years towards developing composite prognostic scoring systems and moving away from the traditional binary approach to risk stratification. The traditional approach focuses on the top performing variable(s) while discounting the additive or cumulative effect of a combination of different predictor variables. Composite risk scores, which combine the level of risk across a number of variables, have become more commonplace. The advantage of such an approach is that it allows the quantification of risk across the spectrum of abnormal responses. Increasingly, these models are beginning to utilise more data derived from CPET. For example, the Hull CPET risk score was recently developed by our laboratory. We found that individual predictors of mortality ranged from 0.60 to 0.71 (Harrell's C statistic), but the optimal combination of EOV + $\text{VE}/\dot{V}\text{CO}_2$ slope + OUES + VEqCO_2 nadir reached 0.75 in patients with mild-to-moderate CHF. The Hull CPET risk score had a significantly higher area under the curve (0.78) when compared to the Heart Failure Survival Score ($\text{AUC}=0.70$; $P<0.001$) (Ingle et al., 2014). Our findings indicate that data derived solely from CPET outperforms traditional prognostic risk markers which are collected from a range of different

investigations. CPET appears to be a time efficient and cost effective modality for stratifying risk in patients with CHF.

Patient case study

Table 4 summarises the results of a CPET performed by a patient who attended our exercise laboratory for risk stratification and CRF assessment. The patient was a 62 year-old male (body mass index of $32\text{kg}\cdot\text{m}^{-2}$) in normal sinus rhythm with an unremarkable ECG. The patient complained of dyspnoea on light exertion and had recently been diagnosed with coronary heart disease and undergone elective percutaneous coronary intervention. Incremental CPET on a treadmill was performed and breath-by-breath cardiorespiratory data collected (averaged over 15 seconds). A maximal effort was confirmed as the patient met two of the criteria in box 2.

The patient's failure to achieve at least 75% of his predicted $\dot{V}\text{O}_{2\text{max}}$ (Wasserman et al., 2011) was consistent with reduced CRF (Guazzi et al., 2012). Using standard exercise tolerance test criteria, his 12-minute test duration would have been considered 'normal'. The reduction in CRF may have been due to severe deconditioning, however this was excluded as his VAT was within the normal range ($>40\%$ actual/predicted $\dot{V}\text{O}_{2\text{peak}}$). Data were therefore suggestive of respiratory or cardiac limitation. Pre-test spirometry values from 3 reproducible attempts were within normal range and peak exercise breathing reserve ($\text{VE}_{\text{max}}/\text{estimated maximal voluntary ventilation}$) was also $>20\%$ suggesting adequate ventilation for the exercise intensity (Balady et al., 2010). The probability that respiratory disease was underlying exercise limitation was therefore deemed unlikely.

The rise in O_2/HR was blunted coinciding with a significantly steepened VO_2/HR relationship suggesting SV limitation. This pattern of LV dysfunction during exercise is consistent with myocardial ischaemia. Both the OUES and VAT were pseudo-normal, but were suggestive of a reduction in O_2 transport/utilisation. The $\text{VE}/\dot{V}\text{CO}_2$ slope however, was significantly elevated (>34) indicating inefficient ventilation and importantly, poor prognosis (30% likelihood of suffering a cardiac event within three years (Arena et al., 2007b). The most likely cause of the $\text{VE}/\dot{V}\text{CO}_2$ slope elevation was circulatory limitation, given the attenuation

of O_2/HR and compensatory response of HR in relation to $\dot{V}\text{O}_2$ needed to sustain Q. The absence of any overt respiratory abnormality during spirometry; normal breathing reserve at peak exercise; history of PCI; and moderately reduced ejection fraction at rest support the conclusion that the patient's exercise limitation was due to an underlying circulatory limitation.

Conclusion

The intention of this guide is to provide a concise, uncomplicated evidence based summary of CPET and present an approach to data interpretation for clinical decision-making. For this reason, detailed description of patient preparation procedures and technical aspects of equipment calibration/test conduction is beyond the scope of this guide. We recommend that readers review other key publications providing guidance for CPET (Balady et al., 2010, American Thoracic Society/American College of Chest Physicians, 2003).

CPET is a safe, non-invasive assessment of cardiorespiratory function. It allows the determination of key prognostic variables and can distinguish pathophysiology not apparent at rest. It is able to discriminate cardiovascular, ventilatory and peripheral limitations during exercise by monitoring disturbances in key variable responses ($\dot{V}\text{O}_2$, VE, $\dot{V}\text{CO}_2$ and HR). CPET offers additional interpretive power over conventional stress testing and thus can lead to improved clinical decision-making and risk stratification in patients with cardiometabolic and respiratory disease.

5 KEY POINTS

- Multiple factors (circulatory, ventilatory and metabolic) contribute to exercise intolerance across a wide spectrum of patients with cardiovascular disease. Establishing the aetiology and prognostic importance of exercise intolerance is a significant challenge for clinicians.
- Cardiopulmonary exercise testing allows the determination of a number of powerful prognostic markers widely accepted in clinical practice

- Protocols that involve small to modest work rate increments per stage are preferred since they better preserve the relationship between oxygen uptake and work rate.
- Multiple factors can affect exercise intolerance and a methodical approach to eliminating specific possible causes should be adopted.
- Cardiopulmonary exercise testing offers a more comprehensive assessment of cardiorespiratory function than exercise tolerance tests and has been shown to have good sensitivity and specificity in the detection of exercise-induced myocardial ischaemia.

Table 4: A cardiopulmonary exercise test report showing key variables for our patient case study

Patient Information			
Gender: Male		Age: 61	
Height: 174.7cm	Weight: 97Kg	BMI: 31.67kg/m ²	Waist-Hip Ratio: 1.06
Blood Pressure: 100/78mmHg		Pulse: 61bpm – Sinus Rhythm	
Past Medical History: PCI, Obesity, Gout		Smoker: Yes- 20 per day	
Current Medications: Aspirin, Clopidogrel, Bisoprolol, Simvastatin, GTN Spray		Reported Symptoms: Shortness of breath on exertion	
Spirometry Results			
PEF	7.6 ‡		
FVC	4.39 ‡		
FEV ₁	3.4 ‡		
FEV ₁ /FVC Ratio	0.77 ‡		
eMVV	136		
Breathing Reserve	44 ‡		
CPET Results			
Test Duration	Minutes: 12 ‡	Seconds: 1	
Criteria for Maximum Testing	HR ≥ 85% predicted HR max (age & β-Blocker adjusted) ‡		
Test Termination Criteria	Leg fatigue & inability to maintain required work rate		
VO _{2peak}	20.6ml/Kg ⁻¹ (79.8% predicted maximum) ●		
Peak HR	130bpm (83% of predicted maximum) ◇		
VAT	13.5ml/Kg ⁻¹ (66% VO _{2peak} , 52% Predicted VO _{2peak})		
OUES	1.9 ◇		
VE/VCO ₂ Slope	42.19 ●		
O ₂ /HR	Blunted rise at 1minute 57 seconds ●		
VO ₂ /HR Relationship	Elevated at 4 minutes and 28 seconds ●		
ST Segment Depression	1.8mm ◇		

Chest Pain	Nil ‡
Breathing Reserve at Peak Exercise	22% ‡

‡ = Within normal range; ◊ = Pseudo normal; ● = Abnormal

BMI = Body mass index; PCI = Percutaneous coronary intervention; GTN, Glyceryl trinitrate; PEF = Peak expiratory flow; FVC = Forced vital capacity; FEV₁ = Forced expiratory volume in 1 second; eMVV = estimated maximal voluntary ventilation; HR = Heart rate; VAT = Ventilatory anaerobic threshold; OUES = Oxygen uptake efficiency slope; VE = Minute ventilation; VCO₂, expired carbon dioxide; VO_{2peak} = peak oxygen uptake

References

- AARONSON, K. D., SCHWARTZ, J. S., CHEN, T.-M., WONG, K.-L., GOIN, J. E. & MANCINI, D. M. 1997. Development and Prospective Validation of a Clinical Index to Predict Survival in Ambulatory Patients Referred for Cardiac Transplant Evaluation. *Circulation*, 95, 2660-2667.
- AGOSTONI, P., CORRA, U., CATTADORI, G., VEGLIA, F., BATTALIA, E., LA GIOIA, R., SCARDOVI, A. B., EMDIN, M., METRA, M., SINAGRA, G., LIMONGELLI, G., RAIMONDO, R., RE, F., GUAZZI, M., BELARDINELLI, R., PARATI, G., MAGRI, D., FIORENTINI, C., CICOIRA, M., SALVIONI, E., GIOVANNARDI, M., MEZZANI, A., SCRUTINIO, D., DI LENARDA, A., MANTEGAZZA, V., RICCI, R., APOSTOLO, A., IORIO, A., PAOLILLO, S., PALERMO, P., CONTINI, M., VASSANELLI, C., PASSINO, C. & PIEPOLI, M. F. 2013. Prognostic value of indeterminable anaerobic threshold in heart failure. *Circ Heart Fail*, 6, 977-87.
- AMERICAN THORACIC SOCIETY/AMERICAN COLLEGE OF CHEST PHYSICIANS 2003. ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine*, 167, 211.
- ARENA, R., MYERS, J., ABELLA, J. & PEBERDY, M. A. 2005. Influence of heart failure etiology on the prognostic value of peak oxygen consumption and minute ventilation/carbon dioxide production slope. *CHEST Journal*, 128, 2812-2817.
- ARENA, R., MYERS, J., ABELLA, J., PEBERDY, M. A., BENSIMHON, D., CHASE, P. & GUAZZI, M. 2007a. Development of a ventilatory classification system in patients with heart failure. *Circulation*, 115, 2410-2417.
- ARENA, R., MYERS, J., HSU, L., PEBERDY, M. A., PINKSTAFF, S., BENSIMHON, D., CHASE, P., VICENZI, M. & GUAZZI, M. 2007b. The Minute Ventilation/Carbon Dioxide Production Slope is Prognostically Superior to the Oxygen Uptake Efficiency Slope. *Journal of Cardiac Failure*, 13, 462-469.
- BABA, R., NAGASHIMA, M., GOTO, M., NAGANO, Y., YOKOTA, M., TAUCHI, N. & NISHIBATA, K. 1996. Oxygen uptake efficiency slope: A new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *Journal of the American College of Cardiology*, 28, 1567-1572.
- BALADY, G. J., ARENA, R., SIETSEMA, K., MYERS, J., COKE, L., FLETCHER, G. F., FORMAN, D., FRANKLIN, B., GUAZZI, M., GULATI, M., KETEVIAN, S. J., LAVIE, C. J., MACKO, R., MANCINI, D., MILANI, R. V., ON BEHALF OF THE AMERICAN HEART ASSOCIATION EXERCISE, C. R., CARDIOLOGY, P. C. O. T. C. O. C., EPIDEMIOLOGY, C. O., PREVENTION, DISEASE, C. O. P. V., CARE, I. C. O. Q. O. & RESEARCH, O. 2010. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation*, 122, 191-225.
- BANNER, N. R., BONSER, R. S., CLARK, A. L., CLARK, S., COWBURN, P. J., GARDNER, R. S., KALRA, P. R., MCDONAGH, T., ROGERS, C. A. & SWAN, L. 2011. UK guidelines for referral and assessment of adults for heart transplantation. *Heart*, 97, 1520-1527.
- BEAVER, W. L., WASSERMAN, K. & WHIPP, B. J. 1986. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol*, 60, 2020-2027.
- BELARDINELLI, R., LACALAPRICE, F., CARLE, F., MINNUCCI, A., CIANCI, G., PERNA, G. & D'EUSANIO, G. 2003. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J*, 24, 1304-13.
- BENSIMHON, D. R., LEIFER, E. S., ELLIS, S. J., FLEG, J. L., KETEVIAN, S. J., PIÑA, I. L., KITZMAN, D. W., MCKELVIE, R. S., KRAUS, W. E., FORMAN, D. E., KAO, A. J., WHELLAN, D. J., O'CONNOR, C. M. & RUSSELL, S. D. 2008. Reproducibility of Peak Oxygen Uptake and Other Cardiopulmonary Exercise Testing Parameters in Patients With Heart Failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise traiNing). *The American Journal of Cardiology*, 102, 712-717.

- CARTER, R., AL-RAWAS, O., STEVENSON, A., MCDONAGH, T. & STEVENSON, R. 2006. Exercise responses following heart transplantation: 5 year follow-up. *Scottish medical journal*, 51, 6-14.
- CHAUDHRY, S., ARENA, R., WASSERMAN, K., HANSEN, J. E., LEWIS, G. D., MYERS, J., CHRONOS, N. & BODEN, W. E. 2009. Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing. *The American Journal of Cardiology*, 103, 615-619.
- DAVIES, L. C., WENSEL, R., GEORGIADOU, P., CICOIRA, M., COATS, A. J. S., PIEPOLI, M. F. & FRANCIS, D. P. 2006. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *European Heart Journal*, 27, 684-690.
- DEKERLE, J., BARON, B., DUPONT, L., VANVELCENAHAR, J. & PELAYO, P. 2003. Maximal lactate steady state, respiratory compensation threshold and critical power. *European journal of applied physiology*, 89, 281-288.
- GITT, A. K., WASSERMAN, K., KILKOWSKI, C., KLEEMANN, T., KILKOWSKI, A., BANGERT, M., SCHNEIDER, S., SCHWARZ, A. & SENGES, J. 2002. Exercise Anaerobic Threshold and Ventilatory Efficiency Identify Heart Failure Patients for High Risk of Early Death. *Circulation*, 106, 3079-3084.
- GUAZZI, M., ADAMS, V., CONRAADS, V., HALLE, M., MEZZANI, A., VANHEES, L., AHA, ARENA, R., FLETCHER, G. F., FORMAN, D. E., KITZMAN, D. W., LAVIE, C. J. & MYERS, J. 2012. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *European Heart Journal*, 33, 2917-2927.
- GUAZZI, M., PALERMO, P., PONTONE, G., SUSINI, F. & AGOSTONI, P. 1999. Synergistic efficacy of enalapril and losartan on exercise performance and oxygen consumption at peak exercise in congestive heart failure. *The American journal of cardiology*, 84, 1038-1043.
- GUAZZI, M., REINA, G., TUMMINELLO, G. & GUAZZI, M. D. 2004. Improvement of alveolar-capillary membrane diffusing capacity with exercise training in chronic heart failure. *Journal of applied physiology*, 97, 1866-1873.
- HOLLENBERG, M. & TAGER, I. B. 2000. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *Journal of the American College of Cardiology*, 36, 194-201.
- INGLE, L. 2007. Theoretical rationale and practical recommendations for cardiopulmonary exercise testing in patients with chronic heart failure. *Heart Fail Rev*, 12, 12-22.
- INGLE, L., GOODE, K., CARROLL, S., SLOAN, R., BOYES, C., CLELAND, J. G. F. & CLARK, A. L. 2007. Prognostic value of the VE/VCO₂ slope calculated from different time intervals in patients with suspected heart failure. *International Journal of Cardiology*, 118, 350-355.
- INGLE, L., ISTED, A., WITTE, K. K., CLELAND, J. G. & CLARK, A. L. 2009. Impact of different diagnostic criteria on the prevalence and prognostic significance of exertional oscillatory ventilation in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil*, 16, 451-456.
- INGLE, L., RIGBY, A. S., SLOAN, R., CARROLL, S., GOODE, K. M., CLELAND, J. G. & CLARK, A. L. 2014. Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart*, 100, 781-786.
- INGLE, L., SLOAN, R., CARROLL, S., GOODE, K., CLELAND, J. G. & CLARK, A. L. 2011. Prognostic significance of different measures of the ventilation-carbon dioxide relation in patients with suspected heart failure. *European Journal of Heart Failure*, 13, 537-542.
- MALFATTO, G., FACCHINI, M., BRANZI, G., BRAMBILLA, R., FRATIANNI, G., TORTORICI, E., BALLA, E. & PEREGO, G. B. 2005. Reverse ventricular remodeling and improved functional capacity after ventricular resynchronization in advanced heart failure. *Italian heart journal: official journal of the Italian Federation of Cardiology*, 6, 578-583.
- MANCINI, D. M., EISEN, H., KUSSMAUL, W., MULL, R., EDMUNDS, L. H. & WILSON, J. R. 1991. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*, 83, 778-786.

- MEZZANI, A., AGOSTONI, P., COHEN-SOLAL, A., CORRÀ, U., JEGIER, A., KOUIDI, E., MAZIC, S., MEURIN, P., PIEPOLI, M., SIMON, A., LAETHEM, C. V. & VANHEES, L. 2009. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention & Rehabilitation*, 16, 249-267.
- MEZZANI, A., HAMM, L. F., JONES, A. M., MCBRIDE, P. E., MOHOLDT, T., STONE, J. A., URHAUSEN, A. & WILLIAMS, M. A. 2013. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *European Journal of Preventive Cardiology*, 20, 442-467.
- SULLIVAN, M. J., HIGGINBOTHAM, M. B. & COBB, F. R. 1988. Increased exercise ventilation in patients with chronic heart failure: intact ventilatory control despite hemodynamic and pulmonary abnormalities. *Circulation*, 77, 552-559.
- TAYLOR, C., NICHOLS, S. & INGLE, L. 2015. A clinician's guide to cardiopulmonary exercise testing 1: an introduction. *Br J Hosp Med (Lond)*, 76, 192-5.
- VAN DE VEIRE, N. R., VAN LAETHEM, C., PHILIPPÉ, J., DE WINTER, O., DE BACKER, G., VANDERHEYDEN, M. & DE SUTTER, J. 2006. VE/Vco₂ slope and oxygen uptake efficiency slope in patients with coronary artery disease and intermediate peakVo₂. *European Journal of Cardiovascular Prevention & Rehabilitation*, 13, 916-923.
- VAN LAETHEM, C., DE SUTTER, J., PEERSMAN, W. & CALDERS, P. 2009. Intratest reliability and test-retest reproducibility of the oxygen uptake efficiency slope in healthy participants. *European Journal of Cardiovascular Prevention & Rehabilitation*, 16, 493-498.
- WASSERMAN, K., HANSEN, J., SUE, D., STRINGER, W., SIETSEMA, K., SUN, X.-G. & WHIPP, B. 2011. *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications*, Philadelphia, Wolters Kluwer Health/Lippincott Williams & Wilkins.
- WEBER, K. T., KINASEWITZ, G. T., JANICKI, J. S. & FISHMAN, A. P. 1982. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. *Circulation*, 65, 1213-1223.
- WHIPP, B. J., HIGGINBOTHAM, M. B. & COBB, F. C. 1996. Estimating exercise stroke volume from asymptotic oxygen pulse in humans. *Journal of Applied Physiology*, 81, 2674-2679.